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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/021,660	02/10/1998	MARGARET H. BARON	1874/110	4751

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EXAMINER
KAUFMAN, CLAIRE M

ART UNIT	PAPER NUMBER
1646	36

DATE MAILED: 04/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/021,660	Applicant(s) BARON ET AL.	
	Examiner Claire M. Kaufman	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-75 and 82-113* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-75 and 82-113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed 2/01/02 has been entered.

Response to Arguments

The rejection of claims under 35 USC 112, second paragraph, is withdrawn in view of the amendment to the claims.

The enablement rejection under 35 USC 112, first paragraph, has been recast to reflect the changes introduced by the amendment to the claims. Claims 58, 59, 84, 97 and 98 are no longer rejected due to the amendment to the independent claims and the limitation to naturally occurring Ihh, Dhh or Shh in these claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The amendment filed 8/27/01 remains objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The sequences and description of sequence properties added from WO 95/18856 represent new matter because they were added by improper incorporation by reference (see above). The description of % identity or homology to sequences and hybridization as newly set forth is also new matter. (See previous Office action, paragraph bridging pages 3-4.)

Applicant is required to cancel the new matter in the reply to this Office Action.

Applicant argues that the specification does not merely refer to WO 95/18856, but expressly incorporates it by reference in the specification as filed, "including ...hedgehog proteins..." which "may be selected for modulating hematopoiesis ...according to the assays of the invention", and points to a specific portion defined by subject matter of the prior application instead of defined by line and column number. The argument has been fully considered, but is not persuasive. Incorporation of a portion based solely on subject matter is not proper

incorporation by reference. The subject matter relating to WO 95/18856 described in the instant specification is extremely broad, encompassing any protein related in any manner (functionally or structurally) to a "hedgehog protein", which itself is has not limiting definition (*i.e,* is not limited to Ihh, Shh or Dhh obtainable from nature) (original p. 22, lines 14-23). Proper incorporation requires specific attention be direct to the portion to be incorporated, not to the subject matter to be incorporated.

Applicant argues that as interpreted through *Telemac Cellular v Topp Telecom, Application of Lund* and *Advanced Display Sys. v. Kent State*, the entire document is considered incorporated, so any part of the document is necessarily incorporated. The argument has been fully considered, but is not persuasive. While the entire document is incorporated, and any portion thereof to which specific attention has been drawn may be included in the incorporating application by amendment, this is distinct from the instant situation in which no specific portion had been identified.

Applicant argues that the MPEP is a reference only and is not case law. The argument has been fully considered, but is not persuasive. The MPEP relies on the legal basis set forth in the *In re Hawkins* (CCPA 1973) decisions cited (MPEP 608.01(p), see previous Office action), the material that was deemed to be properly incorporated was identified as material with a very specific chemical structure (*e.g.,* 197 USPQ 164, first col., second paragraph from the bottom). In the instant situation, the equivalent would be if the original disclosure had incorporated the SEQ ID NO:35-42 of to WO 95/18856 and structural relatedness by a particular range of percent identities. This would be a material specifically referred to without the need to state line and column or page number. Instead, the instant application as originally filed contained a general, vague and widely encompassing reference.

Additionally, it is noted that in *In re Hawkins*, 179 USPQ 161, 486 F.2d 579 (CCPA 1973), case law from *In re Argoudelis*, 58 CCPA 769, 434 F.2d 1390, 168 USPQ 99 (1970) is discussed as follows:

> Further, for the satisfaction of the second aspect of section 112—that of establishing the filing date as the prima facie date of invention—"it is essential that there be no question that, *at the time an application for patent is filed,* the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than

ordinary skill and reasonably time, remain in order to obtain an operative, useful embodiment)."

As can be seen from the enablement rejection under 35 USC 112, set forth in the previous Office action on pages 4-7, the material Applicants seek to incorporate from WO 95/18856, would not provide a enabling disclosure.

Claim Objections

Claim 74 remains objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Both claim 74 and claim 72 from which it depends have the claim limitation of the same modes of administration (see previous Office action on page 4.)

Applicant argues that no such claim 74 is pending because of claim renumbering and were cancelled. The argument has been fully considered, but is not persuasive. Claim renumbering began at claim 80 (see previous Office action, second paragraph. Claim 74 (and 75) were never renumbered and never cancelled. Note the amendment after final of 7/9/01 was never entered. The pending claims are claims 57, 73, 83, 85, 88, 95, 96 and 113 filed 2/1/02; 58-72, 82, 84, 86, 87, 89-94, 97-112 (as renumbered) filed 8/27/01; and claims 74 and 75 filed 3/3/00.

Claim Rejections - 35 USC § 112, First Paragraph

Claims 57-75 and 82-113 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the previous Office action on page 4, and as discussed in the sections entitled "Incorporation by Reference".

Applicant's arguments of this issue were presented and discussed above in the section entitled "Incorporation by Reference".

Claims 57, 58, 60-75 and 82, 83, 85-96 and 99-113 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stimulating a population of undifferentiated mammalian mesodermally derived cells to undergo hematopoiesis or of stimulating hematopoiesis in an animal, comprising contacting said cells or administering to the animal, respectively, an effective amount of Ihh, Dhh or Shh protein or a fragment thereof which binds to patched and induces cells to undergo hematopoiesis such that the protein or fragment thereof contacts or would reasonably be expected to contact undifferentiated mammalian mesodermally derived cells or hematopoietic stem cells, does not reasonably provide enablement for administration wherein the protein or fragment thereof does not specifically contact the above cell types and wherein the protein or fragment is not Ihh, Dhh, Shh or a fragment thereof which binds to patched and induces cells to undergo hematopoiesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons set forth in the previous Office action on pages 4-7.

Applicant argues that claim 83 does not need to specify cell type contacted for enablement. This argument is persuasive in part. Claim 83 is no longer rejected on the basis of administration on cell contact, however, it is still rejected based on the compounds used in the method (at least 80% identical to SEQ ID NO:34-40 or a fragment thereof).
Applicant argues that because i) there is about 85% cross-species identity, ii) the previous Office action acknowledges that Shh, Ihh and Dhh would all be expected to function in the disclosed method, iii) a mouse Shh gene, Hhg-1 functions in Drosophila (Chang et al., of record) even though only 46% Hhg-1 and drosophila hh are only about 46% identical, and Dryer et al., Dev. 2001, shows that human hh proteins used were used in mice in experiments relating to hematopoiesis, then one skilled in the art would expect many non-mammalian hh proteins to functionally replace mammalian hh proteins represented by the SEQ ID Nos., especially in view of the disclosure of WO 95/18856, which discusses the portions of various hh proteins that

contribute to the biological activity of this family of signaling molecules. The argument has been fully considered, but is not persuasive. Even though there is about 85% cross-species identity between mammalian Shh, there is lower identity between mammalian and other Shh and also between Sonic and other hh proteins. While between mammalians the skilled artisan would reasonably expect that Ihh, Dhh and Shh could function in the claimed methods, this is not true for methods using animals other than mammals or hh proteins not obtainable from nature. It is acknowledged that Shh does share some functions with Ihh and Dhh, but this does not mean all functions are share, including stimulation of hematopoiesis. For a system to display complete—even three times overlapping—redundancy of a myriad of functions as is being suggested in Applicants response for hh proteins, would be such the exception to the rule it would be highly unexpected by one skilled in the art. Even if a mouse Shh functions in a drosophila, that it has not been shown to be involved in hematopoiesis is significant. Nor does the cross-species functioning provide guidance as to what specific parts of the structure would be necessary to carry out the instant invention. Providing a general sequence (*e.g.* consensus sequence like SEQ ID NO:42 or one 80% identical to SEQ ID NO:37) with two functional limitations is inviting experimentation without a reasonable expectation of what structures would provide those functions in the instant claims. Further, the teachings of Dryer et al. again support intra-mammalian use of hedgehog proteins obtainable from nature, but do not provide basis for the wide breadth of compounds recited in the claims when linked to very particular functions they are required to display. WO 95/18856 does not point to more than N-terminal or C-terminal portions of naturally occurring hh proteins that have activity. There is no disclosure of specifically which amino acids are necessary for particular activities such as stimulation of hematopoiesis. Therefore, the art--present and past—does not provide sufficient enabling support for the breadth of the claims as they stand.

Applicants argue that the Examiner has not provided any support in the form of references for the rejection. This is not correct. See p. 6, middle paragraph, and p. 7, second paragraph. Further, art is not required if the rejection is based on sound scientific reasoning. Typically references show only positive not negative findings. There is no art of showing of record of mutations of human Shh, for example, which show the variety of non-naturally occurring sequences that can induce hematopoiesis.

Applicant argues that the VEGF and hh pathways do not seem to be related, and that applicants hh proteins *do* induce hematopoiesis. The Shalaby et al.(Nature 1995) reference is intended to show that even though receptor activation may be responsible for a particular physiological effect, what particular effect a ligand for that receptor will have is not necessarily predictable. Altering a known ligand can produce an inactive or antagonistic ligand. Williams et al. (J. Cell Sci., 1999 Dec. : 112 (Pt. 23) : 4405-14, abstract only) showed that some N-terminally truncated Shh proteins bound patched-1, but unlike wildtype Shh failed to promote hh-dependent cell differentiation.

Applicants argue that WO 95/18856 provides detailed techniques for making and testing variant sequences as well as discussing methods such as combinatorial mutagenesis. Also the present application provides assays for testing variants, so that even though a broad variety of compounds is encompassed by the claims, it would not require undue experimentation to make a representative number and that the art of record shows that significant variability can be tolerated. The argument has been fully considered, but is not persuasive. Making and testing is not the standard for enablement. As discussed above, the art shows limited examples of variation—only those hh that occur in nature—as well as supporting a very limited reasonable expectation of shared function by all naturally occurring hh. What is provided is an invitation to experiment. It is not predictable whether all naturally occurring hh proteins from all organisms can function in the claimed method, and even less predictable about what proteins with related but non-naturally occurring hh structures would reasonably be expected to function in the claimed invention for the reasons discussed in the previous Office action and above.

Applicants argue claim 75 does not use the term "synergistically". The argument has been fully considered, but is not persuasive. Please see the section above entitled "Claim Objection" for a discussion of the pending claims. There is an obvious discrepancy between Applicant's and Examiner's list of pending claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646
April 18, 2002

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER